Myocarditis in Clinical Practice

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Abstract

Myocarditis is a polymorphic disease characterized by great variability in clinical presentation and evolution. Patients presenting with severe left ventricular dysfunction and life-threatening arrhythmias represent a demanding challenge for the clinician. Modern techniques of cardiovascular imaging and the exhaustive molecular evaluation of the myocardium with endomyocardial biopsy have provided valuable insight into the pathophysiology of this disease, and several clinical registries have unraveled the disease's long-term evolution and prognosis. However, uncertainties persist in crucial practical issues in the management of patients. This article critically reviews current information for evidence-based management, offering a rational and practical approach to patients with myocarditis. For this review, we searched the PubMed and MEDLINE databases for articles published from January 1, 1980, through December 31, 2015, using the following terms: *myocarditis*, *inflammatory cardiomyopathy*, and *endomyocardial biopsy*. Articles were selected for inclusion if they represented primary data or were review articles published in high-impact journals. In particular, a risk-oriented approach is proposed. The different patterns of presentation of myocarditis are classified as low-, intermediate-, and high-risk syndromes according to the most recent evidence on prognosis, clinical findings, and both invasive and noninvasive testing, and appropriate management strategies are proposed for each risk class.

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Myocarditis is an inflammatory disease of the myocardium diagnosed using established histologic and immunohistochemical criteria (Table 1) (Figure 1).[1-3] A recently published position statement by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases provides updated recommendations regarding the etiology, diagnosis, and therapeutic management of myocarditis.[3] However, despite the formally structured definition, myocarditis is a heterogeneous disease, characterized by extensive variability in clinical presentation and ensuing evolution.[4] This variability necessitates patient-tailored diagnostic and therapeutic management in which the advanced and often costly testing and treatments are reserved for those with the most severe and threatening clinical presentation. In fact, gaps persist between published recommendations and clinical practice, while real-world, applicable, hands-on guidelines for the practical management of the various manifestations of myocarditis are lacking.

Accordingly, this review summarizes the contemporary knowledge about myocarditis, offering a rational and practical approach for the management of this polymorphic disease. For this purpose, we searched the PubMed and MEDLINE databases for articles published from January 1, 1980, through December 31, 2015, using the following terms: *myocarditis*, *inflammatory cardiomyopathy*, and *endomyocardial biopsy*. Articles were selected for inclusion if they represented primary data or were review articles published in high-impact journals. In particular, a clinically oriented classification based on events risk is proposed. The different patterns of presentation of myocarditis are classified as low-, intermediate-, and high-risk syndromes according to the most recent evidence on prognosis, clinical findings, and both invasive and noninvasive testing, and appropriate management strategies are proposed for each risk class.

ETIOLOGY AND EPIDEMIOLOGY

Myocarditis can be triggered by different causes: infections (ie, viruses, bacteria, parasites), autoimmune diseases, hypersensitivity, high catecholamine states, drugs, toxic

ARTICLE HIGHLIGHTS

- Myocarditis is an inflammatory disease of the myocardium characterized by great heterogeneity of presentation and evolution. The main patterns of clinical presentation are chest pain, arrhythmias, and heart failure, and disease severity may range from asymptomatic or mild self-limiting syndromes to severe life-threatening scenarios requiring intensive hemodynamic support.
- Patients presenting with chest pain and/or supraventricular arrhythmias with preserved left ventricular function typically have an excellent prognosis (low-risk syndromes). Conversely, patients presenting with heart failure and/or life-threatening arrhythmias, in particular when associated with severe left ventricular dysfunction, have a consistent probability of major clinical events in long-term follow-up, and their prognosis largely depends on the short-term response to therapy (high-risk syndromes).
- Several cases exist with intermediate characteristics between low- and high-risk syndromes (patients with mild to moderate ventricular dysfunction, frequent nonsustained ventricular arrhythmias, persistent regional wall motion and/or electrocardiographic anomalies, presence of late gadolinium enhancement). These patients merit particular attention both in the diagnostic work-up and in follow-up because their prognosis is largely unknown.
- A critical and integrated evaluation of clinical and instrumental noninvasive investigations (clinical history, electrocardiography, echocardiography, cardiac magnetic resonance imaging) is fundamental for the identification of cases of suspected myocarditis. However, the definite diagnosis of myocarditis is provided by histologic and immunohistochemical analysis of myocardial tissue samples obtained with an endomyocardial biopsy.
- The diagnostic work-up and clinical management of patients with suspected or confirmed myocarditis should be tailored on the basis of the severity of clinical presentation and response to medical therapy. Invasive diagnostic testing, such as endomyocardial biopsy, and specific therapies, like immunosuppression, should be reserved for patients presenting with major clinical syndromes (severe heart failure and/or life-threatening arrhythmias) that are refractory to conventional therapies.
- A structured follow-up is crucial in the management of patients with myocarditis. The interval between each reevaluation and the duration of the follow-up should be tailored on the basis of the severity of clinical presentation, the extent of ventricular remodeling, and subsequent risk of events.

substances, or physical agents.[5] Once other specific causes are ruled out, most cases of myocarditis observed in clinical practice are attributable to viral infections and/or immune reactions. In particular, even when no viruses are detected by serologic and polymerase chain reaction (PCR) analyses, an unrecognized viral infection remains the most probable cause of idiopathic myocarditis. These cases are presumably observed in an advanced phase (usually 3 or 4 weeks after the infection) when the immune system has already achieved a complete clearance of the virus.[5]

In consideration of the broad spectrum of clinical presentations, it is difficult to establish the actual epidemiological burden of myocarditis in the real world because its prevalence changes considerably in relationship to the population under study and to the adopted diagnostic criteria. For example, a recent epidemiological study identified myocarditis as the final diagnosis for 0.5% of all hospital admissions for cardiovascular reasons, frequently affecting a young population of mainly male patients.[6] However, previous studies detected myocarditis on endomyocardial biopsy (EMB) in 10% to 17% of patients with otherwise unexplained cardiomyopathy.[7,8] Similarly, myocarditis was found in 5% of individuals in a series of unselected and consecutive autopsies, but the disease was considered the main cause of death in only a minority.[9] In this sense, it appears that myocarditis is underdiagnosed. Yet, it is obvious that the histopathologic characterization of this condition is not always necessary and gains practical relevance only in selected cases.

TABLE 1. Criteria for the Definition of Myocarditis

Histologic criteria[1]: evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of nonischemic origin
Immunohistochemical criteria[3]: abnormal inflammatory infiltrates defined as >14 leukocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of >7 CD3-positive T lymphocytes/mm^2

CLINICAL PRESENTATION AND DIAGNOSIS

The heterogeneity of clinical presentation of myocarditis ranges from subclinical, or benign, forms to major clinical syndromes, such as severe heart failure or life-threatening ventricular arrhythmias.[4] In most cases, the clinical expression of myocarditis can be exemplified by 3 main patterns of presentation[4,10]: (1) recent-onset heart failure (<6 months), (2) arrhythmias, and (3) chest pain. According to the position statement on the diagnosis and management of myocarditis from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, the clinical suspicion of myocarditis should arise in each of the aforementioned scenarios when the major contribution of other disease conditions, such as coronary heart disease, valvular heart disease, congenital heart disease, or hypertensive cardiomyopathy, has been excluded.[3]

Of importance, the suspicion of myocarditis should take into consideration the mode of clinical presentation and some instrumental features at baseline and at short-term follow-up. These characteristics in fact could be useful tools in the prognostic stratification of patients with myocarditis in order to guide their further optimal management. As an implementation of current recommendations,[3] this review proposes a practical and clinically oriented classification based on events risk.

Figure 2 illustrates the following 3 risk classes and the proposed clinical management:

(1) High-risk major clinical syndromes. Prognosis largely depends on the short-term response to therapy and the evolution of clinical and functional parameters (eg, the presentation of recent-onset severe heart failure with severe left ventricular dysfunction and/or life-threatening arrhythmias).
(2) Low-risk syndromes. These cases are typically characterized by a good long-term prognosis (eg, the presentation of chest pain and/or supraventricular arrhythmias with preserved left ventricular function and rapid [within 1-4 weeks] complete resolution of the electrocardiographic (ECG) and echocardiographic abnormalities).
(3) Intermediate-risk syndromes. Although most cases of myocarditis are classified as high- or low-risk syndromes, some are characterized by the presence of structural or functional abnormalities, such as mild to moderate ventricular dysfunction, persistent wall motion or ECG abnormalities, late gadolinium enhancement in the absence of severe left ventricular dysfunction and remodeling on cardiac magnetic resonance imaging, or frequent nonsustained ventricular arrhythmias, that place them in a gray zone of prognostic uncertainty.

Typical findings for each risk scenario are provided in Supplemental Figures 1, 2, and 3 (available online at http://www.mayoclinicproceedings.org).

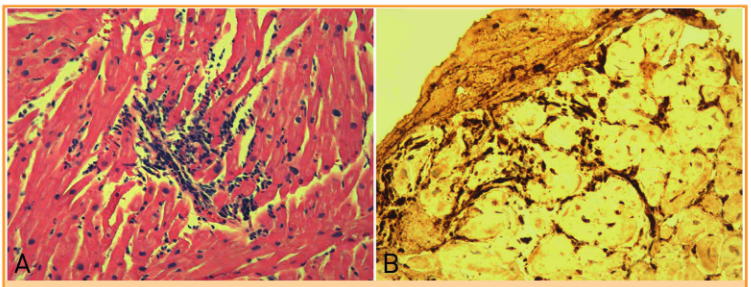

FIGURE 1. Photomicrographs of active lymphocytic myocarditis (A, hematoxylin-eosin, original magnification ×20; B, immunohistochemical staining for HLA-DR antigen, original magnification ×20). Courtesy of Rosssana Bussani, MD, Institute of Pathological Anatomy and Histology, Ospedali Riuniti and University of Trieste.

ROLE OF NONINVASIVE AND INVASIVE DIAGNOSTIC TESTING

The diagnostic work-up of myocardial inflammatory syndromes should be tailored to the severity of clinical/instrumental presentation and the short-term response to medical therapy (Figure 2).

Noninvasive Testing

Several noninvasive diagnostic tests with varying diagnostic potential and accuracy are available to clinicians for the diagnostic work-up of suspected myocarditis (Table 2). Personal

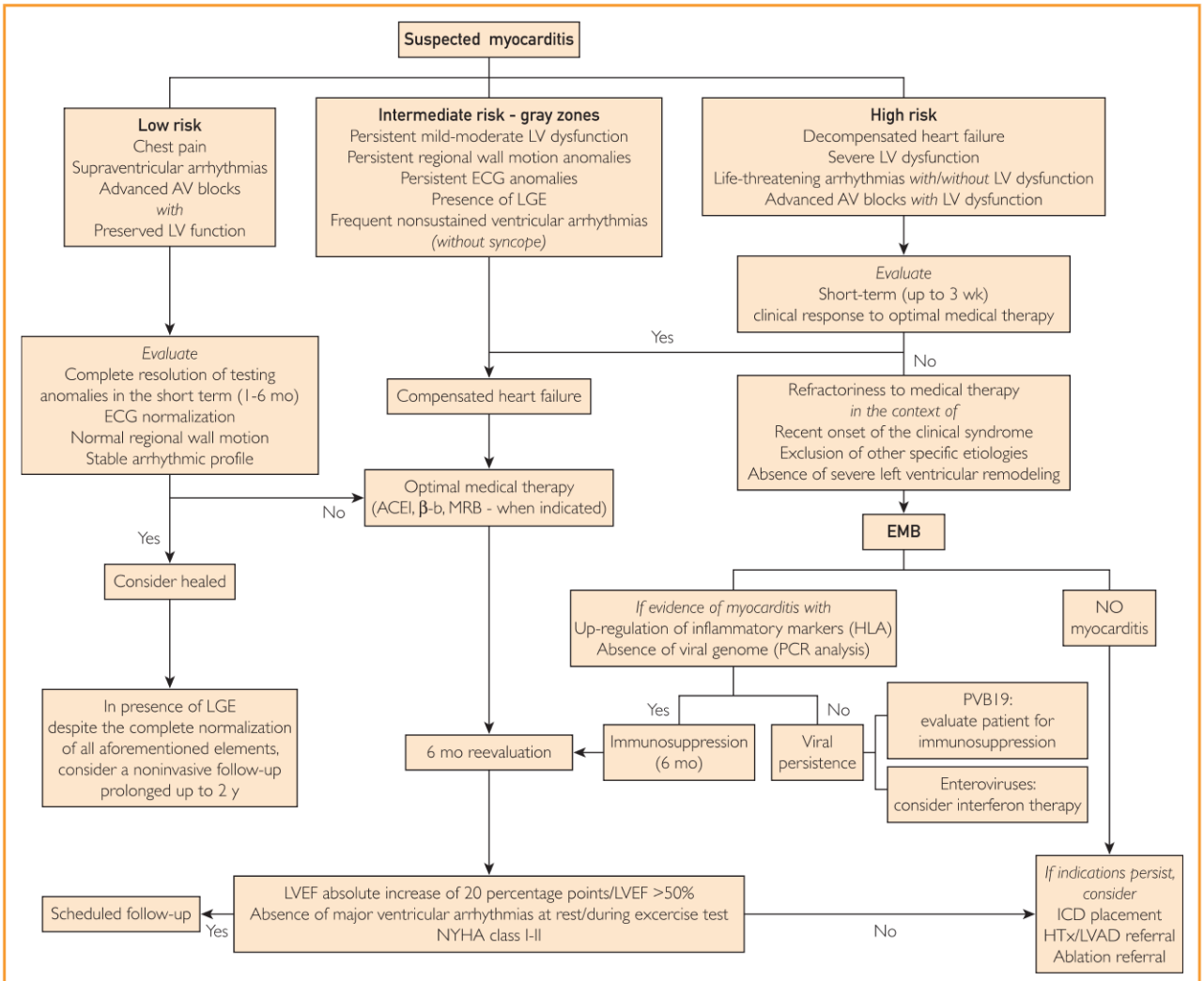

FIGURE 2. Proposal for clinical management of patients with suspected myocarditis. ACEI = angiotensin-converting enzyme inhibitor; AV = atrioventricular; β-b = β-blocker; ECG = electrocardiographic; EMB = endomyocardial biopsy; HLA = HLA antigen; HTx = heart transplant; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVAD = LV assist device; LVEF = LV ejection fraction; MRB = mineralocorticoid receptor blocker; NYHA = New York Heart Association; PCR = polymerase chain reaction; PVB19 = parvovirus B19.

history, together with ECG, biomarkers, Holter monitoring, and echocardiographic features, should be thoroughly evaluated once other possible causes (ie, coronary artery disease, hypertensive heart disease, valve diseases) are excluded (Table 2). Once patients are classified into low-, intermediate-, or high-risk categories according to their clinical presentation, second-level examinations for the diagnosis of myocarditis should be undertaken.

In this sense, cardiac magnetic resonance imaging represents the criterion standard for the morphological/functional evaluation of cardiac structures and the characterization of the myocardial tissue, providing useful diagnostic and prognostic information in various clinical settings.[10-12] However, cardiac magnetic resonance imaging has accessibility limitations and modest diagnostic accuracy in some clinical presentations, such as high- and intermediate-risk forms (Table 2).[22] Furthermore, cardiac magnetic resonance imaging is poorly applicable in the presence of frequent ventricular and atrial arrhythmias.

TABLE 2. Role and Typical Findings of Noninvasive Testing and Endomyocardial Biopsy in the Diagnostic Work-up of Myocarditis

Variable	Low risk	Intermediate risk	High risk
Personal history	Should always be thoroughly investigated[4,10,11] Flulike symptoms, insect bite (for *Borrelia* or *Rickettsia* suspicion), timing of symptoms onset, family history of cardiomyopathy, drugs or toxic substances assumption		
Biomarkers	Troponin: typically elevated (no prognostic value)[12,13]	Troponin: low accuracy for detection of myocardial inflammation[14]	
	Antimicrobial serology: • low accuracy for detection of myocardial infection[15] • not to be routinely considered in the diagnostic work-up • may be useful to detect infections by *Borrelia* or *Rickettsia* in presence of clinical suspicion for bradyarrhythmias and advanced AV blocks Serologic analyses for autoimmune diseases should be considered only in the presence of clinical suspicion		
Electrocardiography	Diffuse and saddle-shaped ST-segment elevation Bradyarrhythmias or advanced AV conduction defects in the absence of LV dysfunction may be suggestive of infections by *Borrelia* or *Rickettsia*	Low voltages Discordance between the severity of the clinical scenario and the scarcity of electrocardiographic alterations (absence of left atrial dilation and left intraventricular conduction delay) Bradyarrhythmias or advanced AV conduction defects in the presence of LV dysfunction may be suggestive of sarcoidosis or giant cell myocarditis	
Echocardiography	Normal ventricular dimensions, morphologic features, wall motion, and global function Transient wall motion anomalies Transient mild ventricular dysfunction Pericardial effusion[4,12,13]	Global impairment of LV or biventricular function without major remodeling Diastolic dysfunction Patchy alterations of the wall motion not responsive to coronary distribution or electrocardiographic alterations Pericardial effusion Transient pseudohypertrophy of the ventricular wall Alteration of the echocardiographic myocardial texture[4,16,17]	
Cardiac magnetic resonance imaging	Good accuracy[11,18-20] Distinction between myocarditis and acute coronary syndromes (subepicardial vs subendocardial/transmural LGE distribution)[18]	Modest accuracy[14,21] May be considered a conclusive diagnostic test	Modest accuracy[14,21] Cannot be considered a conclusive diagnostic test in the context of a major clinical syndrome
Coronary angiography/computed tomography	In case of risk factors for coronary artery disease	In case of risk factors for coronary artery disease	Indicated
Endomyocardial biopsy	Not indicated	May be considered (case by case selection)	Indicated in the presence of refractoriness to medical therapy in the short term

AV = atrioventricular; LGE = late gadolinium enhancement; LV = left ventricular.

Endomyocardial Biopsy

Histopathologic analysis of myocardial tissue samples collected with EMB is the only way to definitively diagnose myocarditis.[1] International recommendations about EMB implementation in clinical practice are controversial. The American College of Cardiology/American Heart Association guidelines[23,24] recommend EMB in patients with severe clinical presentation in terms of recent heart failure or life-threatening arrhythmias. Conversely, the position statement on the diagnosis and management of myocarditis by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases expanded the spectrum of EMB indications, recommending this test for all cases of clinically suspected myocarditis regardless of the pattern and severity of clinical presentation.[3]

In clinical practice, the value of EMB becomes crucial in detecting the specific histotype of the myocarditis and assessing the immunologic and virologic status of the myocardium through immunohistochemical and biomolecular PCR analyses. In this sense,

EMB allows tailoring of therapy to the individual patient.[25,26] However, EMB is invariably characterized by a mild, but not negligible, rate of major complications (around 1%) even when performed by experienced operators.[27-29] Moreover, EMB has well-known limitations in its accuracy.[30] Hence, EMB should be performed for the in-depth evaluation of recent-onset high-risk major clinical syndromes not responding to standard optimized medical therapy in the short term (from hours to 3 weeks after admission, on the basis of clinical status severity) (Table 3). In such cases, the definite EMB-driven diagnosis of myocarditis can offer additional information for clinical management: the in-depth characterization of the myocardial substrate can in fact provide the guide for a biopsy-driven therapeutic plan. Conversely, the value of EMB is questionable in patients presenting with low-risk syndromes and responding to standard care with no prospect of therapeutic or prognostic implication. Finally, in the setting of intermediate-risk syndromes, EMB should be considered on a case by case basis according to the clinical status of the patient and the presence of extensive structured myocardial involvement.

When EMB is performed, it is crucial to collect a sufficient number of tissue samples ($\geq$4).[31] Although there are no clear recommendations, in our experience a biventricular approach is preferred,[27,31] pending the procedural feasibility in the individual patient (eg, presence of left ventricular thrombosis or intra-aortic balloon pump). No clear evidence exists on the possible usefulness of cardiac magnetic resonance imaging in selecting the site of biopsy.[27] Finally, it is crucial to ensure the appropriate preservation of the biopsy material and its subsequent evaluation in order to obtain the most exhaustive information from traditional histopathologic, immunohistochemical, and molecular virologic examination.[32]

NATURAL HISTORY AND PROGNOSTIC STRATIFICATION

Myocarditis is characterized by a highly variable natural history, ranging from quick resolution, to relapse, to the development of dilated cardiomyopathy and heart failure or unexpected sudden cardiac death.[4] Thus, the identification of reliable early predictors of long-term prognosis is crucial for clinical management. A concise summary of the results of the main clinical trials and prospective studies reporting data on the outcome of myocarditis are reported in the Supplemental Table (available online at http://www.mayoclinicproceedings.org).

High-Risk Syndromes

It is well known that myocarditis is associated with severe and refractory heart failure generally characterized by poor prognosis, with a 60% heart transplant–free survival at 10-year follow-up.[4,10] In particular, acute hemodynamic instability,[33-35] intraventricular conduction abnormalities,[36] and extensive structural derangement of the ventricular myocardium detected on late gadolinium enhancement at cardiac magnetic resonance imaging coexisting with left ventricular remodeling and dysfunction have emerged as early independent predictors of long-term prognosis.[37]

Nevertheless, an important variability exists among these patients regarding the further disease course, ranging from the complete recovery of ventricular function to progression to dilated cardiomyopathy. In fact, myocarditis represents a model of potentially reversible cardiomyopathy, and spontaneous or therapeutically induced improvement of ventricular function occurs within a few months after the onset of symptoms in 40% to 50% of patients initially presenting with left

TABLE 3. Indications for Endomyocardial Biopsy

Severe congestive heart failure
Severe left ventricular dysfunction
Life-threatening ventricular arrhythmias
In the context of
Recent onset of the clinical syndrome
Refractoriness to conventional treatment in the short term (from hours to 3 wk after admission on the basis of clinical status severity)
Exclusion of other specific etiologies
Absence of severe left ventricular remodeling
Suspecting
Severe lymphocytic myocarditis
Giant cell myocarditis: major ventricular arrhythmias, atrioventricular blocks, autoimmune disorders, thymoma, drug hypersensitivity
Necrotizing eosinophilic myocarditis: ventricular thrombosis, hypereosinophilic syndromes, drug hypersensitivity
Cardiac sarcoidosis: major ventricular arrhythmias, atrioventricular blocks, extracardiac sarcoidosis

ventricular systolic dysfunction.[4,38] The improvement of left ventricular function in the short term (defined as an absolute increase of 20% in the left ventricular ejection fraction or left ventricular ejection fraction >50% 6 months after the first evaluation) has emerged as a predictor of favorable long-term prognosis, independent from baseline left ventricular function.[4] Yet, the identification of clinically useful predictors of rapid improvement remains challenging.[4] In this regard, magnetic resonance imaging is a promising tool because the absence of late gadolinium enhancement appears to be a strong predictor of left ventricular reverse remodeling in the setting of idiopathic dilated cardiomyopathy.[39] Finally, a prospectively scheduled short-term follow-up increases the accuracy of long-term prognostic stratification of these patients because it is fundamental to assess the disease evolution in response to therapy (Table 4).

Few data are available regarding the prognosis for patients presenting with major arrhythmic instability. The available evidence indicates an intermediate risk of major events during long-term follow-up.[4] In particular, patients presenting with marked signs of ventricular derangement, such as persistent ECG or wall motion abnormalities, severe ventricular functional impairment, or extensive burden on late gadolinium enhancement, seem to be at higher risk for recurrence of major arrhythmic events during midterm follow-up.[40] However, because no reliable prognostic predictors have been identified for this subgroup of patients, a structured program of clinical and instrumental short-term reevaluation appears appropriate for the long-term management of these patients.

Low-Risk Syndromes

Patients presenting with chest pain, normal left ventricular function without wall motion abnormalities, stable arrhythmic profile, and complete resolution of ECG abnormalities in the short term can be considered definitively healed, with excellent long-term prognosis (Table 4).[4,10,12,13]

The presence of troponin release is not prognostically relevant in the context of myopericardial inflammatory syndromes and thus should not itself be a reason for a prolonged follow-up or additional investigation.[13] Cardiac magnetic resonance imaging is an accurate tool in diagnostic work-up of this group of patients (Table 2). However, the presence of subepicardial late gadolinium enhancement, typically present in this condition, does not seem convincingly related to a worse prognosis when associated with preserved ventricular wall motion and a stable arrhythmic profile.[13] Future studies in this peculiar setting are needed in order to confirm these findings. As mentioned previously, EMB does not appear to be indicated in the context of low-risk myocarditis.

Intermediate-Risk Syndromes

Despite the clear distinction between low-risk and high-risk syndromes, many patients still present with clinical, morphological, or functional features of prognostic uncertainty in which clinical decisions are not supported by the existing evidence. For instance, little

TABLE 4. Proposal for the Scheduled Follow-up of Patients With Myocarditis

Variable	Low risk	Intermediate risk	High risk
Time of clinical reevaluations	1 mo, 6 mo, 2 y	3 mo, 6 mo, 12 mo, then yearly	3 wk, 3 mo, 6 mo, 12 mo, then yearly
Noninvasive testing	Assess ECG and echocardiographic normalization between 1 and 6 mo. Cardiac MRI is recommended	Periodic evaluation of LVEF and LV remodeling (ECG) Periodic evaluation of the arrhythmic burden (Holter monitoring) Annual evaluation of arrhythmia induction during exercise test Cardiac MRI with LGE evaluation, if not assessed at disease presentation	
Exercise restriction	Yes, for 2 y	Yes, lifetime	Yes, lifetime
Lifetime follow-up	No, if normalization at 2 y	Yes	Yes
Lifetime therapy	No, if normalization at 2 y	Yes	Yes

ECG = electrocardiography; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = LV ejection fraction; MRI = magnetic resonance imaging.

evidence is available regarding patients presenting with chest pain and diffuse wall motion abnormalities, mild to moderate left ventricular dysfunction, or persistent ECG abnormalities. Data are also lacking for patients with frequent nonsustained ventricular arrhythmias and extensive late gadolinium enhancement in the absence of severe left ventricular dysfunction and remodeling. In these cases, prolonged clinical and instrumental follow-up is recommended because these findings may reflect the extensive myocardial derangement potentially leading to late arrhythmias or future evolution to left ventricular remodeling (Table 4). Notably, EMB may be helpful in the diagnostic work-up of this group of patients when findings on cardiac magnetic resonance imaging cannot be considered conclusive. In particular, EMB could be useful in diagnosing cardiac sarcoidosis or giant cell myocarditis allowing to plan an appropriate therapeutic management.[7,27]

THERAPEUTIC ISSUES

Conventional and Supportive Therapy

The therapeutic management of myocarditis should be based on the pattern and severity of the clinical presentation, the short-term response to conventional treatments, and spontaneous or therapeutically induced improvement. The main pattern of presentation, ie, heart failure, arrhythmias, and myopericardial inflammatory syndromes, should be treated with standard therapeutic regimens.

In the context of active myocarditis associated with severe left ventricular dysfunction, major clinical decisions, such as referral for heart transplant, left ventricular assist device, or prophylactic implantable cardioverter-defibrillator, should be deferred for 3 or 6 months, if feasible, and reevaluated according to short-term evolution under optimal medical treatment.[4]

Few data are available on myocarditis presenting with life-threatening or incessant ventricular tachyarrhythmias. In such cases, the indication for implantable cardioverter-defibrillator therapy is unclear and should be evaluated on an individual basis according to clinical presentation (eg, aborted sudden cardiac death or syncope), the magnitude of structural-functional ventricular derangement (eg, ventricular remodeling, presence of akinetic segments or aneurysmal deformation, extent of late gadolinium enhancement), the histopathologic substrate (eg, cardiac sarcoidosis or giant cell myocarditis), and therapeutic response to standard care.[4,40] Likewise, referral for ablation should be considered in cases of persistent ventricular arrhythmias despite optimal medical therapy and identification of a structured substrate after excluding the inflammatory triggers.

Immunomodulating Therapy

Although numerous interventions targeting components of viral and immune responses (eg, immunosuppression,[25,26,41] antiviral drugs,[42] and intravenous immunoglobulin[43]) have been tested, none of them have been proved to impact survival. However, several small studies in well-selected patients found favorable effects in terms of ventricular function and clinical improvement,[25,26] paving the way for ensuing well-designed, larger randomized controlled trials.

Immunosuppressive therapy with prednisone and azathioprine appears suitable for patients with EMB-proven active myocarditis with major clinical symptoms such as heart failure with severe ventricular dysfunction and/or life-threatening ventricular arrhythmias in whom conventional treatments have failed in the short term of 7 to 10 days. In this setting, the histopathologic diagnoses of giant cell myocarditis, necrotizing eosinophilic myocarditis, or cardiac sarcoidosis represent a clear indication for immunosuppressive therapy.[30] Notably, current evidence suggests that in patients with lymphocytic myocarditis, immunosuppressive treatment should be administered only in the presence of increased tissue inflammatory markers[25] and the absence of a viral genome,[26] as identified on immunohistochemical and PCR analyses of myocardial samples.

Currently, the importance of a persisting viral genome in myocardial samples is strongly debated because of conflicting findings.[10,33,42,44] In particular, controversies are focused on the role of parvovirus B19 that recently emerged as an endemic virus encountered with similar frequency in almost half of patients with perimyocarditis,[45] dilated

cardiomyopathy,[46] or other noninflammatory heart diseases.[47-49] The full understanding of the role of parvovirus B19 and other viruses is crucial because currently, the presence of the viral genome in the myocardium detected by PCR represents a contraindication to immunosuppressive therapy for patients who would otherwise be clinical candidates. In such cases, a careful evaluation of the individual patient is mandatory. It is critical to cautiously consider the suitability of immunosuppression in cases with major clinical syndromes, refractoriness to maximal conventional therapy, and the absence of coronary vasculitis or viremia in blood samples.

Although there is a potential role for interferon treatment in the context of myocarditis with evidence of enteroviral infection,[42] no randomized data are available regarding the effect of such therapy in all patients with myocarditis. Likewise, even though intravenous immunoglobulin treatment has been associated with significant improvement of ventricular function and viral load reduction in dilated cardiomyopathy[44] and appears to prevent relapses in patients with recurrent pericarditis,[50] it has not been validated in inflammatory myopericardial diseases.

Further studies are needed to better evaluate the role of specific antiviral and immunomodulatory treatments in patients with myocarditis and well-characterized virologic and immunologic profiles.

CONCLUSIONS AND KEY POINTS

Myocarditis is an underdiagnosed polymorphic disease with variable clinical presentation, evolution, and prognosis. The diagnostic approach and clinical management should be tailored to the clinical phenotype of the individual patient.

Patients presenting with chest pain and preserved left ventricular function typically have an excellent long-term prognosis and consequently should be managed conservatively. Once all ECG and echocardiographic abnormalities have disappeared during the short-term follow-up, such patients can be considered fully recovered. However, in the presence of extensive subepicardial late gadolinium enhancement despite the complete resolution of such abnormalities, a noninvasive follow-up prolonged up to 2 years is appropriate.

Patients presenting with severe left ventricular dysfunction and life-threatening arrhythmias represent a challenge in terms of diagnosis and clinical management, with some patients requiring advanced medical or mechanical hemodynamic support or even urgent referral for heart transplant. However, in consideration of the potential reversibility of the disease, a frequent reevaluation of clinical and instrumental parameters under optimal medical therapy is crucial for the appropriate management of these patients.

A careful clinical and instrumental evaluation guides the selection of patients at higher risk who could benefit from a comprehensive molecular evaluation of the myocardial substrate with EMB. The EMB-guided diagnostic work-up could guide the further tailoring of immune-interfering therapies. Despite emerging data supporting the use of such therapies in selected patient subsets, the evidence for the prognostic impact of immune-interfering or antiviral therapies is lacking and should be gathered in appropriately designed controlled trials.

ACKNOWLEDGMENTS

We thank Professor Raffale De Caterina, MD, PhD (Institute of Cardiology, G. d'Annunzio University, Chieti, Italy), for his support and motivation.

Abbreviations and Acronyms: **ECG** = electrocardiographic; **EMB** = endomyocardial biopsy; **PCR** = polymerase chain reaction

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